Serial No.: 09/696,194
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Filing Date: 10/26/00
Priority Date: 10/26/99-PROV

# Search Strategy

FILE 'USPATFULL' ENTERED AT 14:04:03 ON 06 DEC 2002

| | | | |
|---|---|---|---|
| | | E | LAVELLE E C/IN |
| L1 | 7 | S | E4-E5 |
| | | E | OHAGAN D T/IN |
| | | E | OHAGAN D T/IN |
| L2 | 322 | S | PLANT LECTIN? |
| L3 | 116 | S | L2 AND ADJUVANT? |
| L4 | 29 | S | L3 AND MUCOSAL |
| L5 | 0 | S | L2 AND (ADJUVANT (5W) LECTIN?) |
| L6 | 1 | S | ADJUVANT (5W) LECTIN? |
| L7 | 43526 | S | (MISTLETOE LECTIN OR ML-1 OR TOMATO LECTIN OR LEA OR PHASEOLU |
| L8 | 8811 | S | L7 AND ADJUVANT? |
| L9 | 759 | S | L8 AND MUCOSAL |
| L10 | 16 | S | L9 AND (MUCOSAL ADJUVANT) |
| L11 | 0 | S | L9 AND (ADJUVANT (10W) MISTLETOE LECTIN) |
| L12 | 0 | S | L9 AND (ADJUVANT (10W) EUROPAEUS) |
| L13 | 0 | S | L9 AND (ADJUVANT (10W) NIGRIN) |
| L14 | 0 | S | L9 AND (ADJUVANT (10W) EBULIN) |
| L15 | 16 | S | L7 AND (MISTLETOE LECTIN) |
| L16 | 0 | S | L7 AND NIGRIN |
| L17 | 65 | S | NIGRIN |
| L18 | 1 | S | L17 AND ADJUVANT |

FILE 'WPIDS' ENTERED AT 14:16:48 ON 06 DEC 2002

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| L19 | 33 | S | PLANT LECTIN? |

FILE 'MEDLINE' ENTERED AT 14:22:17 ON 06 DEC 2002

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| | | E | LAVELLE E C/AU |
| L20 | 18 | S | E2-E3 |
| L21 | 843 | S | PLANT LECTIN? |
| L22 | 1 | S | L21 AND (MUCOSAL ADJUVANT?) |
| L23 | 12 | S | L21 AND ADJUVANT? |
| L24 | 11 | S | L23 NOT L22 |
| L25 | 17 | S | L21 AND (VACCIN? OR IMMUNIZ?) |
| L26 | 15 | S | L25 NOT L23 |
| L27 | 3775 | S | (MISTLETOE LECTIN OR TOMATO LECTIN OR PHASEOLUS VULGARIS OR W |
| L28 | 20 | S | L27 AND ADJUVANT |
| L29 | 19 | S | L28 NOT L23 |

L15 ANSWER 6 OF 16 USPATFULL
2001:126129 Recombinant mistletoe lectin (rML).
Lentzen, Hans, Rosrath, Germany, Federal Republic of
Eck, Jurgen, Heppenheim, Germany, Federal Republic of
Baur, Axel, Meerbusch-Ossum, Germany, Federal Republic of
Zinke, Holger, Bickenbach, Germany, Federal Republic of
Madus Ag Koln, Koln, Germany, Federal Republic of (non-U.S. corporation)
US 6271368 B1 20010807
WO 9701636 19970116
APPLICATION: US 1997-776059 19970619 (8)
WO 1996-EP2773 19960625 19970619 PCT 371 date 19970619 PCT 102(e) date
PRIORITY: EP 1995-109949 19950626
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention relates to nucleic acid molecules encoding preproproteins having after maturation the biological activity of the mistletoe lectin dimer, to vectors comprising these nucleic acid molecules, to hosts transformed with said vectors and to polypeptides and/or polypeptide dimers which are encoded by these nucleic acid molecules. The polypeptides and/or polypeptide dimers of the invention are widely therapeutically applicable. Thus, the present invention further relates to immunotoxins as well as to pharmaceutical compositions that contain the polypeptides and/or the polypeptide dimers of the invention. Additionally, the invention relates to diagnostic compositions comprising the nucleic acid molecules of the invention, the polypeptides and/or the polypeptide dimers of the invention and/or primers which hybridize specifically to the nucleic acid molecules of the invention. Finally, the invention relates to plant protective agents comprising the polypeptides of the invention and/or the polypeptide dimers of the invention.

L19 ANSWER 4 OF 33 WPIDS (C) 2002 THOMSON DERWENT
AN 2001-355455 [37] WPIDS
DNC C2001-110168
TI Use of a mixture of an immunogen and a plant lectin for producing an enhanced immune response, preferably by intranasal administration.
DC B04
IN LAVELLE, E C; O'HAGAN, D
PA (CHIR) CHIRON CORP
CYC 95
PI WO 2001034193 A1 20010517 (200137)* EN 69p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001024712 A 20010606 (200152)
EP 1221972 A1 20020717 (200254) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
ADT WO 2001034193 A1 WO 2000-US41539 20001026; AU 2001024712 A AU 2001-24712 20001026; EP 1221972 A1 EP 2000-988507 20001026, WO 2000-US41539 20001026
FDT AU 2001024712 A Based on WO 200134193; EP 1221972 A1 Based on WO 200134193
PRAI US 1999-161371P 19991026

AB WO 200134193 A UPAB: 20011129
NOVELTY - Use of a mixture of an immunogen and a plant

lectin in a medicament for producing an immune response to the immunogen which is greater than response produced in the absence of the lectin is new.

ACTIVITY - Immunostimulant.

Mice were immunized intranasally on days 1, 14, 28 and 42 and 14 days later samples were collected. A mixture of cholera toxin and ovalbumin gave an IgA titre of 3000 ng/ml compared to 500 ng/ml for ovalbumin alone.

MECHANISM OF ACTION - None given.

USE - The mixture is useful for inducing an immune response in mammals, especially dogs, cats, mice, rats, rabbits, guinea pigs, chimpanzees, baboons and humans.

ADVANTAGE - The mixture provides a simple, effective and non-toxic method of increasing immune responses, especially following mucosal administration.

Dwg.0/22

L20 ANSWER 1 OF 18 MEDLINE
2002626362 Document Number: 22271661. PubMed ID: 12383207. Mistletoe lectins enhance immune responses to intranasally co-administered herpes simplex virus glycoprotein D2. Lavelle E C; Grant G; Pusztai A; Pfuller U; Leavy O; McNeela E; Mills K H G; O'Hagan D T. (Rowett Research Institute, Bucksburn, Aberdeen, UK, Institute of Phytochemistry, University of Witten/Herdecke, Witten, Germany, Department of Biochemistry, Trinity College, Dublin, Ireland, Chiron Corporation, Emeryville, California, USA. ) IMMUNOLOGY, (2002 Oct) 107 (2) 268-74. Journal code: 0374672. ISSN: 0019-2805. Pub. country: England: United Kingdom. Language: English.

AB The mucosal adjuvant properties of the three type 2 ribosome-inactivating proteins (RIPs) from the European mistletoe, Viscum album L., were investigated. Mistletoe lectins were compared with cholera toxin (CT) as adjuvants when delivered nasotracheally together with herpes simplex virus glycoprotein D2 (gD2). All three mistletoe lectins (MLI, MLII, MLIII) were potent mucosal adjuvants. Co-administration of MLI, MLII or MLIII with gD2 led to significantly higher levels of gD2-specific mucosal immunoglobulin A (IgA) and systemic immunoglobulin G (IgG) antibody than when the antigen was delivered alone. The levels of antibodies induced were similar to those generated in mice immunized with gD2 and the potent mucosal adjuvant CT. Administration of ML1 with gD2 enhanced the antigen-specific splenic T-cell proliferative response. Interleukin-5 (IL-5), but not interferon-gamma (IFN-gamma), was detected in supernatants from splenocytes stimulated in vitro with gD2. This indicates that MLI enhanced type 2 T-helper cell (Th2) responses to the bystander antigen, gD2. Analysis of the gD2- and lectin-specific IgG subclass titres in mice immunized with gD2 and MLI, MLII or MLIII revealed a high ratio of IgG1 : IgG2a, which is compatible with the selective induction of Th2-type immune responses.

L20 ANSWER 2 OF 18 MEDLINE
2001560096 Document Number: 21517566. PubMed ID: 11605896. Targeted delivery of drugs to the gastrointestinal tract. Lavelle E C. (Institute for Immunology, Department of Biology, National University of Ireland Maynooth, Co. Kildare.. elavelle@ireland.com) . CRITICAL REVIEWS IN THERAPEUTIC DRUG CARRIER SYSTEMS, (2001) 18 (4) 341-86. Ref: 276. Journal code: 8511159. ISSN: 0743-4863. Pub. country: United States. Language: English.

AB The oral route is attractive for drug administration because it is associated with patient acceptability, less stringent production conditions, and lower costs. However, gastrointestinal destruction of labile molecules and low levels of absorption generally render oral delivery of peptides and proteins ineffective. Several strategies have the potential to enhance the efficacy of orally administered drugs. Bioadhesion is an approach for increasing interaction between drugs and the mucosae. Bioadhesive systems can be nonspecific, achieving adhesion via mechanical processes or specific systems that recognize receptors on epithelial cells. Lectins are one group of specific bioadhesives with many suitable properties for targeting of cells in the gastrointestinal tract (GIT). This review assesses the potential of lectins in the delivery of drugs and vaccines to the GIT.

L20 ANSWER 3 OF 18 MEDLINE
2001134842 Document Number: 21100924. PubMed ID: 11168640. The identification of plant lectins with mucosal adjuvant activity. Lavelle E C; Grant G; Pusztai A; Pfuller U; O'Hagan D T. (Institute for Immunology, Department of Biology, National University of

Ireland, Maynooth, Co. Kildare, Ireland. ) IMMUNOLOGY, (2001 Jan) 102 (1) 77-86. Journal code: 0374672. ISSN: 0019-2805. Pub. country: England: United Kingdom. Language: English.

AB To date, the most potent mucosal vaccine adjuvants to be identified have been bacterial toxins. The present data demonstrate that the type 2 ribosome-inactivating protein (type 2 RIP), mistletoe lectin I (ML-I) is a strong mucosal adjuvant of plant origin. A number of plant lectins were investigated as intranasal (i.n.) coadjuvants for a bystander protein, ovalbumin (OVA). As a positive control, a potent mucosal adjuvant, cholera toxin (CT), was used. Co-administration of ML-I or CT with OVA stimulated high titres of OVA-specific serum immunoglobulin G (IgG) in addition to OVA-specific IgA in mucosal secretions. CT and ML-I were also strongly immunogenic, inducing high titres of specific serum IgG and specific IgA at mucosal sites. None of the other plant lectins investigated significantly boosted the response to co-administered OVA. Immunization with phytohaemagglutinin (PHA) plus OVA elicited a lectin-specific response but did not stimulate an enhanced response to OVA compared with the antigen alone. Intranasal delivery of tomato lectin (LEA) elicited a strong lectin-specific systemic and mucosal antibody response but only weakly potentiated the response to co-delivered OVA. In contrast, administration of wheatgerm agglutinin (WGA) or Ulex europaeus lectin 1 (UEA-I) with OVA stimulated a serum IgG response to OVA while the lectin-specific responses (particularly for WGA) were relatively low. Thus, there was not a direct correlation between immunogenicity and adjuvanticity although the strongest adjuvants (CT, ML-I) were also highly immunogenic.

L20 ANSWER 4 OF 18 MEDLINE
2000118136 Document Number: 20118136. PubMed ID: 10651938. Mucosal immunogenicity of plant lectins in mice. Lavelle E C; Grant G; Pusztai A; Pf]uller U; O'Hagan D T. (Rowett Research Institute, Bucksburn, Aberdeen, UK. ) IMMUNOLOGY, (2000 Jan) 99 (1) 30-7. Journal code: 0374672. ISSN: 0019-2805. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The mucosal immunogenicity of a number of plant lectins with different sugar specificities was investigated in mice. Following intranasal (i.n.) or oral administration, the systemic and mucosal antibody responses elicited were compared with those induced by a potent mucosal immunogen (cholera toxin; CT) and a poorly immunogenic protein (ovalbumin; OVA). After three oral or i.n. doses of CT, high levels of specific serum antibodies were measured and specific IgA was detected in the serum, saliva, vaginal wash, nasal wash and gut wash of mice. Immunization with OVA elicited low titres of serum IgG but specific IgA was not detected in mucosal secretions. Both oral and i.n. delivery of all five plant lectins investigated Viscum album (mistletoe lectin 1; ML-1), Lycospersicum esculentum (tomato lectin; LEA), Phaseolus vulgaris (PHA), Triticum vulgaris (wheat germ agglutinin (WGA), Ulex europaeus I (UEA-1) stimulated the production of specific serum IgG and IgA antibody after three i. n. or oral doses. Immunization with ML-1 induced high titres of serum IgG and IgA in addition to specific IgA in mucosal secretions. The response to orally delivered ML-1 was comparable to that induced by CT, although a 10-fold higher dose was administered. Immunization with LEA also induced high titres of serum IgG, particularly after i. n. delivery. Low specific IgA titres were also detected to LEA in mucosal secretions. Responses to PHA, WGA and UEA-1 were measured at a relatively low level in the serum, and little or no specific mucosal IgA was detected.

L24 ANSWER 3 OF 11 MEDLINE
2001478811 Document Number: 21413449. PubMed ID: 11522395. Probing the

cons and pros of lectin-induced immunomodulation: case studies for the mistletoe lectin and galectin-1. Gabius H J. (Lehrstuhl fur Physiologische Chemie, Tierarztliche Fakultat, Ludwig-Maximilians-Universitat Munchen, 80539 Munich, Germany.. gabius@tiph.vetmed.uni-muenchen.de) . BIOCHIMIE, (2001 Jul) 83 (7) 659-66. Ref: 115. Journal code: 1264604. ISSN: 0300-9084. Pub. country: France. Language: English.

AB When imagining to monitor animal cells through a microscope with resolution at the molecular level, a salient attribute of their surfaces will be the abundance of glycan chains. They present galactosides at their termini widely extending like tentacles into the extracellular space. Their spatial accessibility and their potential for structural variability endow especially these glycan parts with capacity to act as docking points for molecular sensors (sugar receptors such as lectins). Binding and ligand clustering account for transmission of post-binding signals into the cell interior. The range of triggered activities has turned plant lectins into popular tools in cell biology and immunology. Potential for clinical application has been investigated rigorously only in recent years. As documented in vitro and in vivo for the galactoside-specific mistletoe lectin, its apparent immunomodulatory capacity reflected in upregulation of production of proinflammatory cytokines **will not necessarily be clinically favorable but a double-edged sword.** In fact, **lectin application has been shown to stimulate tumor growth in cell lines, histocultures of human tumors and in two animal models using chemical carcinogenesis or tumor transplantation.** When testing immunological effects of the endogenous lectin galectin-1, protection against disorders mediated by activated T cells came up for consideration. Elimination of these cells via CD7-dependent induction of apoptosis, and a shift to the Th2 response by the galectin, are factors to ameliorate disease states. This result encourages further efforts with other galectins. Functional redundancy, synergism, diversity or antagonism among galectins are being explored to understand the actual role of this class of endogenous lectins in inflammation. Regardless of the results of further preclinical testing for galectin-1, these two case studies break new ground in our understanding how glycans as ligands for lectins convey reactivity to immune cells, with impact on the course of a tumor or autoimmune disease.

L31 ANSWER 13 OF 86 MEDLINE
2001541659 Document Number: 21472816. PubMed ID: 11587808. What are the limits of adjuvanticity?. Del Giudice G; Podda A; Rappuoli R. (IRIS Research Center, Chiron SpA, Via Fiorentina 1, 53100, Siena, Italy.) VACCINE, (2001 Oct 15) 20 Suppl 1 S38-41. Journal code: 8406899. ISSN: 0264-410X. Pub. country: England: United Kingdom. Language: English.

AB Vaccines developed traditionally following empirical approaches have often limited problems of immunogenicity, probably due to the low level of purity of the active component(s) they contain. The application of new technologies to vaccine development is leading to the production of purer (e.g. recombinant) antigens which, however, tend to have a poorer immunogenicity as compared to vaccines of the previous generation. The search for new vaccine adjuvants involves issues related to their potential limits. Since the introduction of aluminium salts as vaccine adjuvants more than 70 years ago, only one adjuvant has been licensed for human use. The development of some of these new vaccine adjuvants has been hampered by their inacceptable reactogenicity. In addition, some adjuvants work strongly with some antigens but not with others, thus, limiting their potentially widespread use. The need to deliver vaccines via alternative routes of administration (e.g. the mucosal routes) in order to enhance

their efficacy and compliance has set new requirements in basic and applied research to evaluate their efficacy and safety. Cholera toxin (CT) and labile enterotoxin (LT) mutants given along with intranasal or oral vaccines are strong candidates as mucosal adjuvants. Their potential reactogenicity is still matter of discussions, although available data support the notion that the effects due to their binding to the cells and those due to the enzymatic activity can be kept separated. Finally, adjuvanticity is more often evaluated in terms of antigen-specific antibody titers induced after parenteral immunization. It is known that, in many instances, antigen-specific antibody titers do not correlate with protection. In addition, very little is known on parameters of cell-mediated immunity which could be considered as surrogates of protection. Tailoring of new adjuvants for the development of vaccines with improved immunogenicity/efficacy and reduced reactogenicity will represent one of the major challenges of the ongoing vaccine-oriented research.

L31 ANSWER 33 OF 86 MEDLINE
1999005693 Document Number: 99005693. PubMed ID: 9789264. Molecular basis of vaccination. Del Giudice G; Pizza M; Rappuoli R. (IRIS, Chiron SpA Research Center, Siena, Italy. ) MOLECULAR ASPECTS OF MEDICINE, (1998 Feb) 19 (1) 1-70. Ref: 312. Journal code: 7603128. ISSN: 0098-2997. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Vaccines represent the most cost-effective means to prevent infectious diseases. Most of the vaccines which are currently available were developed long before the era of molecular biology and biotechnology. They were obtained following empirical approaches leading to the inactivation or to the attenuation of microorganisms, without any knowledge neither of the mechanisms of pathogenesis of the disease they were expected to protect from, nor of the immune responses elicited by the infectious agents or by the vaccine itself. The past two decades have seen an impressive progress in the field of immunology and molecular biology, which have allowed a better understanding of the interactions occurring between microbes and their hosts. This basic knowledge has represented an impetus towards the generation of better vaccines and the development of new vaccines. In this monograph we briefly summarize some of the most important biotechnological approaches that are currently followed in the development of new vaccines, and provide details on an approach to vaccine development: the genetic detoxification of bacterial toxins. Such an approach has been particularly successful in the rational design of a new vaccine against pertussis, which has been shown to be extremely efficacious and safe. It has been applied to the construction of powerful mucosal adjuvants, for administration of vaccines at mucosal surfaces.

L31 ANSWER 58 OF 86 MEDLINE
95012932 Document Number: 95012932. PubMed ID: 7927981. AIDS vaccines and adjuvant formulations. Cernescu C E. (St. Nicolau Institute of Virology, Bucharest, Romania. ) INTERNATIONAL JOURNAL OF IMMUNOPHARMACOLOGY, (1994 May-Jun) 16 (5-6) 369-79. Ref: 54. Journal code: 7904799. ISSN: 0192-0561. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The AIDS epidemic is too large to continue ignoring prevention programs that appear to work. In this review the promising experimental immunogens and how close they are to the optimal requirements for a preventive vaccine are presented. Adjuvants and adjuvant formulations (mainly mixtures of adjuvants with suitable vehicles) can help in solving some specific problems of AIDS vaccines: overcome the variable nature of HIV subtypes, generate both antibody and

T-cell response, induce mucosal immunity, avoid enhancing or autoimmune antibodies and distinguish vaccine-induced seropositivity from natural HIV infection. The following categories of adjuvants are discussed: alum, other mineral and bacterial cell-wall derived adjuvants, cytokines, carriers and vehicles. Although many specific mechanisms of the relative effectiveness of adjuvants have been clarified by recent advances in basic immunology the best adjuvant formulation remains largely empirical. A standardized protocol for preclinical testing of adjuvants for AIDS vaccines is a priority task.

L31 ANSWER 77 OF 86 MEDLINE
88110593 Document Number: 88110593. PubMed ID: 3276445. Future prospects for vaccine adjuvants. Warren H S; Chedid L A. (Experimental Immunotherapy, Institut Pasteur, Paris, France. ) CRITICAL REVIEWS IN IMMUNOLOGY, (1988) 8 (2) 83-101. Ref: 170. Journal code: 8914819. ISSN: 1040-8401. Pub. country: United States. Language: English.

AB Since the landmark experiments of Ramon 60 years ago, attempts have been made to augment the humoral and cellular responses to administered antigens in order to develop more potent and less toxic vaccines. The need for an acceptable adjuvant suitable for clinical use has been underscored by recent advances in recombinant biotechnology and synthetic chemistry which have made it possible to create antigens that are smaller and better characterized, yet less immunogenic, than before. It is likely that these antigens will require an adjuvant to achieve protective immunity. Some of these same technological advances, together with a better understanding of the immune system in general, have permitted the study of adjuvants to evolve from an empirical field to a developmental one. This article discusses the currently known agents capable of immunopotentiation and possible strategies for their use in future vaccines.

L38 ANSWER 8 OF 35 MEDLINE
2001654249 Document Number: 21563207. PubMed ID: 11706842. Mechanisms of vaccine adjuvanticity at mucosal surfaces.
Foss D L; Murtaugh M P. (Department of Veterinary PathoBiology, University of Minnesota, St. Paul 55108, USA. ) Anim Health Res Rev, (2000 Jun) 1 (1) 3-24. Ref: 230. Journal code: 101083072. ISSN: 1466-2523. Pub. country: England: United Kingdom. Language: English.

AB The vast majority of pathogens invade via mucosal surfaces, including those of the intestine. Vaccination directly on these surfaces may induce local protective immunity and prevent infection and disease. Although vaccine delivery to the gut mucosa is fraught with obstacles, immunization can be enhanced using adjuvants with properties specific to intestinal immunity. In this review, we present three general mechanisms of vaccine adjuvant function as originally described by Freund, and we discuss these principles with respect to intestinal adjuvants in general and to the prototypical mucosal adjuvant, cholera toxin. The key property of intestinal adjuvants is to induce an immunogenic context for the presentation of the vaccine antigen. The success of oral vaccine adjuvants is determined by their ability to induce a controlled inflammatory response in the gut-associated lymphoid tissues, characterized by the expression of various costimulatory molecules and cytokines. An understanding of the specific molecular mechanisms of adjuvanticity in the gut will allow the rational development of safe and effective oral vaccines.

L38 ANSWER 13 OF 35 MEDLINE

2001423860 Document Number: 21365481. PubMed ID: 11472241. The rational design of vaccine adjuvants for mucosal and neonatal immunization. Mahon B P. (Mucosal Immunology Laboratory, Institute of Immunology, Biology Department, National University of Ireland Maynooth, Co., Kildare, Ireland.. bpmahon@may.ie) . CURRENT MEDICINAL CHEMISTRY, (2001 Jul) 8 (9) 1057-75. Ref: 228. Journal code: 9440157. ISSN: 0929-8673. Pub. country: Netherlands. Language: English.

AB There is an urgent requirement for neonatal vaccines that induce effective and long-lasting immune responses at the mucosal surfaces of the gut and respiratory tract. The delay in their development has been due in part to a lack of understanding of the mucosal and neonatal immune systems. This work reviews recent advances in the understanding of the cells and molecules that mediate immunity, describing the importance of different T helper populations in determining the success of vaccination strategies. These advances have allowed the rational design of novel vaccine adjuvants and delivery systems that can selectively induce immunity at different anatomical sites mediated by distinct T cell populations. Five functional classes of adjuvant are described. These exploit mechanisms which a) create an antigen depot, b) preserve antigen conformation, c) direct antigen to specific immune cells, d) induce mucosal responses and e) induce cytotoxic T cell responses. Comparisons are made between the chemical structures of bacterial toxins and non-toxic derivatives that retain adjuvanticity. The concept of DNA immunization is introduced and the advantages and disadvantages of this novel approach are discussed. The specific problems relating to neonatal immunization are explored with particular reference to the functional immaturity of the neonatal immune system and interference by maternal antibody. Finally, recent work suggesting that there is no intrinsic barrier to designing effective neonatal vaccines deliverable by the mucosal route is discussed.

L38 ANSWER 15 OF 35 MEDLINE
2001400926 Document Number: 21345484. PubMed ID: 11451471. Immunomodulators and delivery systems for vaccination by mucosal routes. Ryan E J; Daly L M; Mills K H. (Institute of Immunology, National University of Ireland, Maynooth, Co., Kildare, Ireland. ) TRENDS IN BIOTECHNOLOGY, (2001 Aug) 19 (8) 293-304. Ref: 105. Journal code: 8310903. ISSN: 0167-7799. Pub. country: England: United Kingdom. Language: English.

AB Current paediatric immunization programmes include too many injections in the first months of life. Oral or nasal vaccine delivery eliminates the requirement for needles and can induce immunity at the site of infection. However, protein antigens are poorly immunogenic when so delivered and can induce tolerance. Novel ways to enhance immune responses to protein or polysaccharide antigens have opened up new possibilities for the design of effective mucosal vaccines. Here, we discuss the immunological principles underlying mucosal vaccine development and review the application of immunomodulatory molecules and delivery systems to the selective enhancement of protective immune responses at mucosal surfaces.

L38 ANSWER 16 OF 35 MEDLINE
2001394145 Document Number: 21150230. PubMed ID: 11251376. Update on antiviral DNA vaccine research (1998-2000). Schultz J; Dollenmaier G; Molling K. (Institute of Medical Virology, University of Zurich, Switzerland. ) INTERVIROLOGY, (2000) 43 (4-6) 197-217. Ref: 162. Journal code: 0364265. ISSN: 0300-5526. Pub. country: Switzerland. Language: English.

AB DNA vaccines can induce protective cellular and humoral immune responses and have therefore been used during the last decade to develop vaccines against a variety of different pathogens. Because current antiviral vaccines predominantly generate humoral immunity, DNA immunization may be especially useful to provide long-term protection against viral diseases that also require cellular immunity (e.g. HIV). A significant number of articles published in the field of DNA vaccines are dealing with viral diseases, reflecting the need for better and alternative vaccination strategies against viruses. The success of DNA immunization depends on a variety of parameters (e.g. type of antigen, method of application and usage of adjuvants). Therefore, different strategies have been explored to modulate the induced immune response with respect to the requirements necessary to protect against a specific pathogen (e.g. induction of mucosal or cell-mediated immunity). The following article provides an update on different aspects of antiviral DNA vaccine research that have previously been reviewed by others.
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L38 ANSWER 19 OF 35 MEDLINE
2001206606 Document Number: 21144824. PubMed ID: 11249641. DNA vaccines--challenges in delivery. Pachuk C J; McCallus D E; Weiner D B; Satishchandran C. (Wyeth-Lederie Vaccines, One Great Valley Parkway, Malvern, PA 19355, USA.. pachukc@war.wyeth.com) . Curr Opin Mol Ther, (2000 Apr) 2 (2) 188-98. Ref: 98. Journal code: 100891485. ISSN: 1464-8431. Pub. country: England: United Kingdom. Language: English.

AB DNA vaccines are typically comprised of plasmid DNA molecules that encode an antigen(s) derived from a pathogen or tumor cell. Following introduction into a vaccine, cells take up the DNA, where expression and immune presentation of the encoded antigen(s) takes place. DNA can be introduced by viral or bacterial vectors or through uptake of 'naked' or complexed DNA. Vaccination with DNA is a recent technology possessing distinct advantages over traditional vaccines (killed or attenuated pathogens) and the more recently developed subunit vaccines. Unlike most subunit vaccines, DNA vaccines induce both the humoral and cellular arms of the immune response. The stimulation of both arms of the immune system is important not only for the prevention of many diseases including AIDS, but also allows the use of a vaccine for therapeutic purposes. While the traditional attenuated pathogen vaccines are also able to elicit both cellular and humoral immune responses, there is a risk of reversion from the attenuated state to the virulent state. This risk does not exist with DNA vaccines. DNA vaccines can be manufactured and formulated by generic processes. DNA vaccine technology, however, is still in its infancy and much research needs to be done to improve the efficiency with which these vaccines work in humans. While continued efforts toward improving both DNA expression and DNA delivery are equally important for increasing the utility of DNA vaccines, this review will focus both on non-viral delivery of plasmid DNA and delivery methods for the encoded antigen.

L38 ANSWER 21 OF 35 MEDLINE
2000426307 Document Number: 20286690. PubMed ID: 10825547. Recent advances in mucosal vaccine development. Chen H. (AstraZeneca R&D Boston, 128 Sidney Street, 02139, Cambridge, MA 02139, USA.. hongming@alum.mit.edu) . JOURNAL OF CONTROLLED RELEASE, (2000 Jul 3) 67 (2-3) 117-28. Ref: 100. Journal code: 8607908. ISSN: 0168-3659. Pub. country: Netherlands. Language: English.

AB Proper stimulation of the mucosal immune system is critical for the effective protection of mucosal surfaces against

colonization and invasion of infectious agents. This requires administration of vaccine antigens directly to various mucosal sites. Due to the low absorption efficiency of mucosally delivered vaccines, however, almost all of the currently marketed vaccines are administered parentally. In addition, sub-optimal immune responses are frequently induced by mucosal immunization and the use of mucosal adjuvants is commonly required. As a result, development of successful mucosal vaccines depends largely on the improvement of mucosal antigen delivery and on the discovery of new and effective mucosal adjuvants. In this review, recent advances in both areas are briefly discussed.

L38 ANSWER 23 OF 35 MEDLINE
1999274472 Document Number: 99274472. PubMed ID: 10344675. Strategies for mucosal vaccine development. Boyaka P N; Marinaro M; Vancott J L; Takahashi I; Fujihashi K; Yamamoto M; van Ginkel F W; Jackson R J; Kiyono H; McGhee J R. (Department of Microbiology, The Immunobiology Vaccine Center, University of Alabama at Birmingham, 35294-2170, USA. ) AMERICAN JOURNAL OF TROPICAL MEDICINE AND HYGIENE, (1999 Apr) 60 (4 Suppl) 35-45. Ref: 117. Journal code: 0370507. ISSN: 0002-9637. Pub. country: United States. Language: English.

AB Vaccines able to induce both secretory IgA for protection of mucosal surfaces and systemic immunity to pathogens invading the host are of great interest in the war against infectious diseases. Mucosal vaccines trigger immune cells in mucosal inductive sites and thus can induce immunity in both the mucosal and systemic compartments. This review presents a critical survey of adjuvants and delivery systems currently being tested for mucosal immunization. A better understanding of cellular and molecular factors involved in the regulation of mucosal immunity will help in the design of safer mucosal vaccines to elicit the appropriate protective immune response to a given pathogen.